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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/66</b>		<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 99/04773</b> <b>(43) International Publication Date:</b> 4 February 1999 (04.02.99)												
<b>(21) International Application Number:</b> PCT/US98/14796 <b>(22) International Filing Date:</b> 17 July 1998 (17.07.98) <b>(30) Priority Data:</b> <table><tr><td>60/053,351</td><td>22 July 1997 (22.07.97)</td><td>US</td></tr><tr><td>60/053,535</td><td>23 July 1997 (23.07.97)</td><td>US</td></tr><tr><td>9717590.5</td><td>20 August 1997 (20.08.97)</td><td>GB</td></tr><tr><td>9717850.3</td><td>22 August 1997 (22.08.97)</td><td>GB</td></tr></table> <b>(71) Applicant (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> DAIFOTIS, Anastasia, G. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). SANTORA, Arthur, C., II [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). YATES, A., John [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). <b>(74) Common Representative:</b> MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).			60/053,351	22 July 1997 (22.07.97)	US	60/053,535	23 July 1997 (23.07.97)	US	9717590.5	20 August 1997 (20.08.97)	GB	9717850.3	22 August 1997 (22.08.97)	GB	<b>(81) Designated States:</b> AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>  <b>(88) Date of publication of the international search report:</b> 15 April 1999 (15.04.99)
60/053,351	22 July 1997 (22.07.97)	US													
60/053,535	23 July 1997 (23.07.97)	US													
9717590.5	20 August 1997 (20.08.97)	GB													
9717850.3	22 August 1997 (22.08.97)	GB													
<b>(54) Title:</b> METHOD FOR INHIBITING BONE RESORPTION  <b>(57) Abstract</b> <p>Disclosed are methods for inhibiting bone resorption in mammals while minimizing the occurrence of or potential for adverse gastrointestinal effects. Also disclosed are pharmaceutical compositions and kits for carrying out the therapeutic methods disclosed herein. The compounds are bisphosphonates selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etridronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, optionally in combination with a histamine H2 antagonist.</p>															

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# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 98/14796

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K31/66

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>SINGER F R ET AL: "Bisphosphonates in the treatment of disorders of mineral metabolism."</p> <p>ADVANCES IN ENDOCRINOLOGY AND METABOLISM, (1995) 6 259-88. REF: 109 JOURNAL CODE: CB4. ISSN: 1049-6734., XP002092145 United States</p> <p>see page 260, paragraph 2 - page 267, paragraph 3; figure 1</p> <p>see page 273, paragraph 3 - page 276, paragraph 3</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	<p>1-28, 30-33</p>



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

3 February 1999

Date of mailing of the international search report

18/02/1999

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

onal Application No

PCT/US 98/14796

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LIBERMAN U A ET AL: "EFFECT OF ORAL ALENDRONATE ON BONE MINERAL DENSITY AND THE INCIDENCE OF FRACTURES IN POSTMENOPAUSAL OSTEOPOROSIS" THE NEW ENGLAND JOURNAL OF MEDICINE, vol. 333, no. 22, 30 November 1995, pages 1437-1443, XP000579307 see abstract</p>	1-28, 30-33
X	<p style="text-align: center;">---</p> <p>BANKHURST A ET AL: "THREE-YEAR TREATMENT WITH ALENDRONATE PREVENTS FRACTURES IN WOMEN WITH POSTMENOPAUSAL OSTEOPOROSIS" ARTHRITIS AND RHEUMATISM, vol. 38, no. 9, SUPPL, 1 September 1995, page S359 XP000579368 see abstract</p>	1-28, 30-33
X	<p style="text-align: center;">---</p> <p>FILIPPONI P ET AL: "CYCLICAL CLODRONATE IS EFFECTIVE IN PREVENTING POSTMENOPAUSAL BONE LOSS: A COMPARATIVE STUDY WITH TRANSCUTANEOUS HORMONE REPLACEMENT THERAPY" JOURNAL OF BONE AND MINERAL RESEARCH, vol. 10, no. 5, May 1995, pages 697-703, XP002042531 see abstract</p>	1,2,6,7, 12,13, 30-33
X	<p style="text-align: center;">---</p> <p>MCCLUNG M R ET AL: "Tiludronate therapy for Paget's disease of bone 'published erratum appears in Bone 1996 Mar;18(3):292!'" BONE, (1995 NOV) 17 (5 SUPPL) 493S-496S. JOURNAL CODE: ASR. ISSN: 8756-3282., XP002092146 United States see abstract</p>	1,2,6,7, 12,13, 30-33
X	<p style="text-align: center;">---</p> <p>SELTENMEYER, Y. ET AL: "A comparison of the antiresorptive potency of various bisphosphonates in vivo with their inhibitory effect in vitro on squalene synthase and cellular sterol synthesis." BONE (NEW YORK), (1997) VOL. 20, NO. 4 SUPPL., PP. 114S. MEETING INFO.: 25TH EUROPEAN SYMPOSIUM ON CALCIFIED TISSUES HARROGATE, ENGLAND, UK APRIL 25-29, 1997 ISSN: 8756-3282., XP002092147 see abstract</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1,2,6,7, 12,13, 30-33

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/14796

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ADACHI J.D.: "osteoporosis-Its Diagnosis, Management and Treatment with New Oral Bisphosphonate Agent, Etidronate" TODAY'S THERAPEUTIC TRENDS, vol. 14, no. 1, 1996, pages 13-24, XP002092148 see abstract see page 19, paragraph 2 - page 21, paragraph 5 ---	1-28, 30-33
X	BELL, NORMAN H. ET AL: "Bisphosphonates in the treatment of osteoporosis" ENDOCRINE (1997), 6(2), 203-206 CODEN: EOCRE5;ISSN: 1355-008X, XP002092149 see abstract ---	1-28, 30-33
X	EP 0 274 158 A (NORWICH EATON PHARMA) 13 July 1988 see claims 1-24; examples 1-8; table 1 ---	1-28, 30-33
X	WO 94 00129 A (PROCTER & GAMBLE PHARMA) 6 January 1994 see claims 1-10; example 5 ---	1-28, 30-33
X	WO 95 08331 A (MERCK FROSST CANADA INC ;BECHARD SIMON R (CA)) 30 March 1995 see page 3, line 13 - page 5, line 23 ---	1-28, 30-33
X	WO 95 28936 A (MERCK & CO INC ;YATES ASHLEY J (US)) 2 November 1995 see abstract -----	1-28, 30-33

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 14796

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 1-29, 33  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds, which are defined by the general definition(s)/formulae used in claims 1,6,7,12,13,18-30,32-33 the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and / or the compounds mentioned in the claims, and to the general idea underlying the application. (see Guidelines, chapter III, paragraph 2.3)

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Original Application No

PCT/US 98/14796

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0274158	A	13-07-1988	AU 616391 B AU 8269487 A CA 1321198 A DE 3789436 D DE 3789436 T DK 670487 A IE 61881 B JP 63239291 A KR 9601845 B PH 26154 A US 5519013 A US 5071840 A US 5334586 A ZA 8709454 A	31-10-1991 23-06-1988 10-08-1993 28-04-1994 25-08-1994 20-06-1988 30-11-1994 05-10-1988 06-02-1996 18-03-1992 21-05-1996 10-12-1991 02-08-1994 10-06-1988
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WO 9528936	A	02-11-1995	US 5646134 A AU 2374895 A BG 100910 A CA 2188030 A CN 1146152 A CZ 9603055 A EP 0756483 A FI 964213 A HR 950239 A HU 74911 A JP 9512268 T NO 964441 A PL 318552 A SK 133396 A ZA 9503185 A	08-07-1997 16-11-1995 31-03-1998 02-11-1995 26-03-1997 11-06-1997 05-02-1997 18-10-1996 30-04-1997 28-03-1997 09-12-1997 18-10-1996 23-06-1997 07-05-1997 27-12-1995